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Resting Coronary Flow Varies With Normal Cardiac Catheter Laboratory Stimuli

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All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

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Abbreviations

APV: Average Peak Flow Velocity

iFR: Instantaneous Wave Free Ratio

FFR: Fractional Flow Reserve

Abstract

Background: Growing evidence supports physiology-guided revascularization, with Fractional Flow Reserve (FFR) the most commonly used invasive measure of coronary blood flow impairment at the time of diagnostic angiography. Recently, there has been growing interest in stenosis severity indices measured at rest, such as Instantaneous Wave Free Ratio (iFR) and the ratio of distal coronary to aortic pressure at rest (resting Pd/Pa). Their reliability may, theoretically, be more susceptible to changes in microvascular tone and coronary flow. This study aimed to assess variability of resting coronary flow with normal catheter laboratory stimuli. **Methods:** Simultaneous intracoronary pressure (Pd) and Doppler Average Peak Flow Velocity (APV) recordings were made at rest and following the verbal warning preceding an intravenous adenosine infusion. Results: 72 patients undergoing elective angiography were recruited (mean age 62 years, 52.7% male) with a wide range of coronary artery disease severity (FFR 0.86 +/- 0.09). Average peak flow velocity varied significantly between measurements at rest and just prior to commencement of adenosine, with a mean variation of 10.2% (17.82+/-9.41 cm/s vs. 19.63+/-10.44cm/s, $p<0.001$) with an accompanying significant drop in microvascular resistance (6.27+/ 2.73 $mmHg.cm^{-1}.s^{-1}$ vs. 5.8+/-2.92 $mmHg.cm^{-1}.s^{-1}$, $p<0.001$). These changes occurred without significant change in systemic hemodynamic measures. Whilst there was a trend for an associated change in the resting indices, Pd/Pa and iFR, this was statistically and clinically not significant (0.92 +/- 0.08 vs. 0.92 +/- 0.08, p=0.110; and 0.90 +/- 0.11 vs. 0.89 +/- 0.12, p=0.073). **Conclusion:** Resting coronary flow and microvascular resistance vary significantly with normal catheter laboratory stimuli, such as simple warnings. The clinical impact of these observed changes on indices of stenosis severity, particularly those measured at rest, needs further assessment within larger cohorts.

Key Words:

Coronary Artery Disease; Fractional Flow Reserve; Instantaneous Wave-Free Ratio

Summary for the annotated table of contents:

Resting coronary flow and microvascular resistance vary significantly with normal catheter laboratory stimuli, such as simple verbal warnings.

Introduction

There is an increasing body of evidence supporting ischemia-guided revascularization compared to coronary angiography alone [1, 2]. This commonly takes the form of pressure-derived estimation of coronary flow impairment within vessels at the time of diagnostic angiography with physiological indices like Fractional Flow Reserve (FFR). FFR is derived by making pressure measurements using pressure transducers that are mounted at the tip of a steerable guidewire to calculate a pressure ratio of coronary pressure distal to a stenosis and aortic pressure (Pd/Pa), at maximal arterial vasodilation (also termed peak hyperemia). This is usually achieved by using pharmacological agents, such as adenosine, to minimize coronary resistance when flow and pressure are approximated to be linear [3]. Measurements of Pd/Pa during hyperemic conditions has been purported to result in improved repeatability with suggested mechanisms being increased spatial resolution and less susceptibility to hemodynamic variability compared to the resting state [4].

In order to overcome the perceived cost, risk and added procedural time of administering adenosine to induce hyperemia, there has been a move to reintroduce resting indices of physiological stenosis severity. Resting pressure-derived indices of coronary blood flow impairment were first used by Andreas Grüntzig et al in 1979 [5] in the form of resting Pd/Pa and has recently evolved to Instantaneous Wave-Free Ratio (iFR), derived from measuring the ratio of Pd/Pa during the proposed 'wave-free period' [6] of diastole. iFR-guided revascularization has demonstrated comparable clinical outcomes to FFR-guided revascularization in two recent non-inferiority randomized controlled trials [7, 8]. The development and use of iFR relies on assumptions that myocardial resistance at rest is maintained at constant levels, particularly in the proposed 'wave-free period' [6], but there continues to be ongoing debate regarding the assumption that myocardial resistance, and

subsequently coronary flow, is constant and minimal within this period [9].

This study aimed to assess the variability of resting microvascular resistance and coronary artery flow velocities in response to normal stimuli within the cardiac catheter laboratory environment, with the premise that the patient and coronary hemodynamics are never truly 'at rest' within the catheter laboratory.

Methods

Patients with stable angina and preserved left ventricular systolic function referred for coronary angiography were recruited into the study. Exclusion criteria were: any contraindication to adenosine; significant valvular disease (greater than mild on echocardiography); recent myocardial infarction (less than 4 weeks), unstable angina, severe 'surgical disease' (left main stem/triple vessel disease) or severe renal impairment. All participants gave written informed consent to participate in *post hoc* analysis of one of several protocols approved by the institutional research ethics committee.

Patients were catheterized via the right radial artery using a standard 6F arterial sheath. Where possible, sedatives such as benzodiazepines and opiates were avoided due to the potential to influence results. Weight-adjusted heparin was administered (70units/kg) intra-arterially. The right and left coronary arteries were intubated using standard Judkins catheters. A 6F Guide catheter was advanced to the aortic root, through which a 0.014'' pressure-flow dual sensor wire (ComboWire XT®, Volcano Corporation, San Diego, CA) was passed with pressure readings calibrated to fluid filled catheter pressure measurements. The tip of the Combowire was then passed beyond the target lesion and manipulated to

optimize the Doppler trace before recording commenced.

All signals were sampled at 200 Hz and stored on disk for off-line analysis. The data were imported into the custom-made Study Manager program (Academic Medical Center, University of Amsterdam, The Netherlands), and at least 5 consecutive beats showing good velocity signals were extracted from each period of interest (good velocity signals identified by an experienced operator from the classic Doppler Envelope and sound emitted from the Doppler sensor). Pan-cardiac cycle analysis was performed on custom-made software, Cardiac Waves (Kings College London, UK). Savitzky–Golay filters were applied to preserve peaks in the data while smoothing [10]. Simultaneous intracoronary pressure and Doppler Average Peak Flow Velocity (APV) were measured at baseline (an average from 1 minute of recording, ~30seconds prior to stimulus). The patient was then given a warning about the commencement of intravenous adenosine, and the possible symptoms they may experience, as per routine clinical practice (the stimulus). Following this, the same measurements were made as those at baseline, just prior to the commencement of intravenous adenosine-induced hyperemia. The pressure sensor was returned to the catheter tip at the end of every recording, to verify that there was no signal drift. If significant drift was noted (±2 mm Hg), measurements were repeated. With these measurements the following indices were calculated:

- Pd/Pa: Ratio of distal coronary pressure (Pd) to aortic pressure (Pa)
- iFR, Instantaneous Wave Free Ratio: Ratio of distal coronary pressure (Pd) to aortic pressure (Pa) during the 'wave free period' in the terminal 75% of diastole. iFR was calculated using the method descried by Sen *et al* [11], using a dedicated software package (CardiacWaves, King's College London, London, UK) that was designed with Matlab (Mathworks, Natick, Massachusetts) and has been previously

validated against propriatery iFR measurements [12]. In addition, we found our iFR data showed strong (R=0.96) and almost identical agreement with measurements made using proprietary software for a selection of cases from this study that had additional validation measurements with the Volcano Veratta wire data [12].

- MR, Microvascular Resistance: calculated as ratio of distal coronary pressure to Average Peak flow velocity [Pd/APV]
- Wave-Free MR, calculated as ratio of distal coronary pressure to Average Peak flow velocity [Pd/APV] during the 'wave-free period' (terminal 75% of diastole, minus the last 5ms)
- BSR, Basal Stenosis Resistance: Ratio of trans-lesional pressure gradient to APV at rest [{Pa-Pd} / APV at rest]

Statistical analyses were performed using IBM SPSS version 24. Normality of data was assessed using histograms and the normal Q-Q plot. Continuous variables are expressed as mean ± SD and compared using paired t-tests or Wilcoxen signed rank test as appropriate. A 2-tailed test for significance was performed in all of the analyses with $P \leq 0.05$ considered as a statistically significant result.

Results

Seventy-two patients referred for angiography for stable angina symptoms were recruited into the study with mean age 61.9 +/- 10.6 years (see Table 1 for patient demographics). As illustrated in table 2, there was no significant change in systemic hemodynamic parameters between the two time-points. In particular there was no significant change in the Rate-

Pressure-Product (RPP), a marker of myocardial oxygen demand (10,400.8 +/- 2,423.2 vs. 10,477.6 +/- 2,599.5, p=0.575).

Average peak flow velocity increased significantly from rest to just prior to commencement of an adenosine infusion with a mean increase of 10.2% (17.82 +/- 9.41 cm/s vs. 19.63 +/- 10.44cm/s, p<0.001). An example trace is shown in Figure 1. This increase in coronary flow was associated with a significant fall in pan-cycle microvascular resistance (6.27 +/- 2.73 $mmHg.cm^{-1}.s^{-1}$ vs. 5.8 +/- 2.92 $mmHg.cm^{-1}.s^{-1}$, p<0.001), and also in the microvascular resistance during the 'wave-free period' (4.48 +/- 2.44 $mmHg.cm^{-1}.s^{-1}$ vs. 4.05 +/- 2.66 $mmHg.cm^{-1}.s^{-1}$, p<0.001). See Table 2.

The mean FFR of patients in the study was 0.86 +/- 0.09. Nineteen of the seventy-two patients recruited (26.4%) were found to have significant obstructive coronary artery disease (defined as FFR<0.8). Based on an iFR threshold of 0.89 to signify obstructive coronary artery disease, 30.6% of lesions were classified as significant. There was no significant difference in the change in APV between the two time points when comparing patients with and without significant coronary artery disease, defined by FFR<0.8 (1.68 +/- 4.33 vs. 1.85 +/- 3.71 respectively, p=0.731). See Figure 2.

The changes in average peak flow velocity and microvascular resistance did not result in significant changes in the resting pressure-derived indices of resting Pd/Pa and iFR (0.92 +/- 0.08 vs. 0.92 +/- 0.08, p=0.110; and 0.90 +/- 0.11 vs. 0.89 +/- 0.12, p=0.073). The resistance index of BSR, also incorporating both pressure and flow velocity, was also unaffected by the changing flow and resistance between the two time-points (0.56 +/- 0.83 vs. 0.52 +/- 0.71, p=0.192) (Table 2).

Discussion

This study demonstrates that resting coronary flow velocity varies with normal cardiac catheter laboratory stimuli, without significant changes in blood pressure and heart rate. The mean 10.2% (1.8cm/sec) change in APV is statistically significant, but whether this small change is of clinical significance is debatable. The statistically significant changes in microvascular resistance, both pan-cycle and wave-free MR, were of larger magnitudes and may be of greater clinical significance.

Recent years has seen the development of and growth of resting, adenosine-independent, indices of stenosis severity. In particular, iFR is growing in popularity with 2 randomized controlled trials showing non-inferior patient outcomes to FFR-guided revascularization. iFR is based on the assertion that microvascular resistance is relatively invariant during the latter part of the diastolic interval, during which the accelerating or decelerating waves identified by wave intensity analysis are minimal. During this period, it is assumed resistance is constant in the absence of hyperemia and that coronary flow is predominantly determined by the passive pressure gradient between the proximal and distal ends of the vessel, analogous to fluid flowing passively through a pipe [11]. This assumption that microvascular resistance is constant and minimal in this 'wave-free period' is often challenged. The VERIFY study and subsequent analysis from Johnson et al. argue this case [9, 16] (although this has subsequently also been challenged by Sen *et al*). In the VERIFY study, iFR values fell significantly following the induction of hyperemia from 0.82 +/- 0.16 vs. 0.64 +/- 0.18 with hyperemia (95 % CI 0.17–0.20; p=0.0001). At an individual level, iFR decreased with

hyperemia in 97 % of the lesions studied with myocardial resistance during the diastolic wave-free period, calculated from simultaneous pressure and flow data, being 250 % higher at rest than during hyperemia [15]. The fact that iFR appeared different during hyperemia versus at rest does not invalidate iFR but shows that resting indices, even those measured during the 'wave-free period' are susceptible to variations in microvascular resistance and coronary peak flow velocity, a surrogate of coronary blood flow. Hence it was important to carry out this study to assess whether true resting conditions can ever be guaranteed in the catheter laboratory.

The results of our study do seem to support the hypothesis that coronary hemodynamics and microvascular tone are never truly at rest within the catheter laboratory with significant variation in coronary flow and microvascular resistance seen from simple instructions. Of interest, the resistance within this wave-free period also varied significantly, challenging the assertion that resistance is constant within the wave-free period (and thereby allowing pressure and flow to approximate linearly for iFR measurements). Whilst we found significant variability in these parameters, it did not result in significant variation in resting Pd/Pa or iFR values, although there was a trend for a statistically significant difference (albeit small and likely clinically unimportant). In addition, we also examined the reliability of Basal Stenosis Resistance (BSR), and again found no significant difference between the resting time-points. Unlike the pressure-derived indices, this resistance index of stenosis severity did not trend towards a statistically significant difference and likely reflects that fact the resistance of a stenosis (by analogy with Ohm's Law, where Resistance = ΔPressure/Flow) is independent of variability in flow conditions [16]. Furthermore, it can be argued form our study that given Pd/Pa, iFR and BSR were all largely unchanged between the two

measurement timepoints, resting indices of coronary stenosis severity may be resilient to the microvascular variability induced by verbal commands.

Coronary blood flow is determined by the intricate interaction of ventricular contractility, heart rate, ventricular compliance, the aortic driving pressure and distal microvascular resistance. Our study suggests that average peak velocity, a surrogate of coronary blood flow, and microvascular resistance can change with normal catheter laboratory stimuli, including simple instructions to the patient that an adenosine infusion is due to start. A potential mechanism for this observation could be subtle variations in myocardial oxygen demand in response to variations in catheter laboratory stimuli. At times of increased oxygen demand (for example during exercise or in response to stressors) supply must also increase up to a point following which ischemia ensues. The major determinant of myocardial oxygen delivery is myocardial blood flow, which is governed by vascular diameter and tone, collateral flow and perfusion pressure [17, 18, 19, 20]. Ischemia develops once these autoregulatory mechanisms are exhausted. In canine models this has been shown to have been predominately achieved through a fall in coronary vascular resistance [21]. Our study supports such a theory, with a similar observed reduction in microvascular resistance and blood flow augmentation. In this study we used RPP as a simple measure of myocardial oxygen demand, but this may not allow appreciation of small changes in myocardial metabolism that may drive the observed changes in coronary flow in response to normal catheter laboratory stimuli. Additionally, in our cohort of relatively mild coronary artery disease (*FFR 0.86 +/- 0.09),* auto-regulatory mechanisms are unlikely to be exhausted. When analyzing the nineteen patients who had FFR<0.80, there was however no significant difference in their APV response to the stimuli (figure 2).

The findings of this study are particularly topical given that revascularization guided by

resting indices has been shown in 2 randomized control trials to be non-inferior to revascularization guided by FFR [7, 8]. In response to these trials, some have suggested that a larger sample size may have shown inferiority of iFR [22] and one of the potential reasons for such a difference could be that resting indices are prone to greater biological variability. Indeed Johnson et al, in their CONTRAST study, showed that the test-retest reliability of resting indices is significantly lower than that of FFR [12]. A potential mechanism for this maybe identified in our study: whereby microvascular resistance in the wave-free period is not constant and there is a trend for baseline variability in resting indices of stenosis severity, albeit of a small magnitude.

In either case, this study provides valuable insight into coronary physiology and how it is prone to variation within a stressful catheter laboratory environment. In our study we investigated changes in flow, pressure-indices and microvascular resistance in response to mild perturbations to the patient. In the catheter laboratory, there are often more stressful and occasionally painful stimuli (for example a full bladder, radial spasm or chest pain) that may potentially have an even larger impact on resting coronary physiology. A more comprehensive larger study would be of value to assess the resting flow variability with different types of stress-inducing stimuli within the catheter laboratory.

Limitations

- This was a small, single-center study with relatively low patient numbers in each group, but it is the first to examine the effects of normal catheter laboratory stimuli on coronary blood flow and microvascular resistance. As a consequence of the relatively small sample size, this study can largely be considered to be a proof-of-concept and hypothesis-generating.

- This study enrolled patients with a relatively mild burden of coronary disease (mean FFR 0.86 +/- 0.09; 19 patients with FFR<0.8). With a wider range of coronary artery disease severity, small changes in MR may unmask an even greater effect on the resting physiology of more severe lesions.
- This study does assume that APV approximates to flow, which in turn assumes a fixed cross sectional coronary vessel area between conditions. We did not attempt to verify this in the current study as techniques such as Quantitative Cross-Sectional Area (QCA) of the vessel at the location of the transducer have too much inherent error to detect potential differences between rest and pre-adenosine states. Nonetheless, all patients were given intracoronary nitrate prior to physiological measurements in an attempt to standardize vessel cross-sectional areas
- Whilst in this study we have shown that resting flow is prone to variability within the Catheter Laboratory environments, there is significant evidence to suggest that hyperemic flow is also prone to a large degree of variability from the effect of various uncontrolled dietary factors on endothelial function (e.g. Long term alcohol[23] and black tea intake[24])'
- Several outlier values in coronary flow velocity (see Figure 2) and microvascular resistance values lead to a non-normal distribution of data in our cohort. Despite this, non-parametric testing confirmed significant differences between rest and verbal stimulus.
- We recognize that measuring Doppler flow velocity is prone to error if clear Doppler envelopes are not achieved. These measurement errors were mitigated by ensuring only the most experienced operators obtained the Doppler flow signals and suboptimal data was excluded from the final analysis. With a meticulous approach, Doppler flow signals have been shown to be highly reproducible in experienced hands

(interclass variability of 0.95 has previously been documented in the absence of external stimuli, with no significant difference between repeated measurements) [25]. Whilst data from this McGinn *et al* study in 1990 is often cited and steps were taken to maintain reproducibility, a modern study on rates of intraobserver and interobserver variability within our center would have strengthened the conclusions drawn from our findings.

Conclusions

Resting coronary flow and microvascular resistance vary significantly with mild cardiac catheter laboratory stimuli, such as a simple warning or instruction, irrespective of hemodynamic status. The small variation observed is statistically significant, but whether it is of clinical significance is debatable. Whilst there was a trend for the commonly used resting indices of stenosis severity (iFR and resting Pd/Pa) to vary with the normal catheter laboratory stimuli, it was statistically non-significant and the magnitude of variability is likely too small to be of clinical significance. This study suggests that evaluation of different types of stress-inducing stimuli within the catheter laboratory, assessed in a larger study and for a wider range of coronary artery disease severity, may be valuable and worth considering.

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Figure Legends

Figure 1: Average Peak Flow Velocity (APV) of a typical case at baseline and following the 'normal catheter laboratory stimulus' of a verbal warning that intravenous adenosine is due to begin.

Figure 2: Bland Altman Plot illustrating the spread of Average Peak Coronary Flow velocity (APV) change. Shaded datapoints represent cases with significant obstructive coronary artery disease, as defined by FFR<0.8. As visualized, APV variability does not depend on APV itself or stenosis severity in this cohort. This was confirmed with a Linear Regression test confirming no significant proportional bias (α (0.05)).

Table 1: Demographics and characteristics of patients recruited into study.

Mean Age	61.9 +/- 10.6
Male (%)	52.7
Diabetes (%)	19.4
Hypertension (%)	61.1
Hypercholesterolemia (%)	68.1
Smoking (%) Current Ex-smoker Never	 19.4 27.8 52.8
Previous myocardial infarction (%)	9.7
Previous percutaneous coronary intervention (%)	16.7
Body mass index (kg/m^2)	29.4 +/- 6.3
Fractional Flow Reserve	0.86 +/- 0.09 (19/72 had FFR≤0.80)
Instantaneous Wave-Free Ratio	0.90 +/- 0.11 (22/72 had iFR≤0.89)

Table 2: Table illustrating difference between Heart Rate (HR), Systolic Blood Pressure (SBP), Rate Pressure Product (HR*SBP), Ratio of distal coronary to proximal aortic pressure (Pd/Pa), Average Peak Coronary Flow Velocity (APV), Microvascular Resistance (MR), Wave Free Microvascular Resistance (MR), Instantaneous Wave Free Ratio (iFR) and Basal Stenosis Resistance (BSR).

	Resting	**Pre-Stimulus**	**P Value**
Heart Rate, bpm	76.85 +/- 14.55	77.80 +/- 15.17	0.283
Systolic Blood Pressure, mmHg	136.31 +/- 25.53	135.43 +/- 25.83	0.322
Rate Pressure Product, mmHg*bpm	10,400.8 +/- 2,423.2	10,477.6 +/- 2,599.5	0.575
APV(U), cms^{-1}	17.82 +/- 9.41	19.63 +/- 10.44	<0.001
APV(U), cms^{-1} when FFR≤0.80	**17.7 +/-13.8**	**19.3 +/- 13.8**	**<0.001**
APV(U), cms^{-1} when iFR≤0.89	**20.6 +/- 13.1**	**22.2 +/- 13.5**	**<0.001**
MR, $mmHg.s.cm^{-1}$	6.27 +/- 2.73	5.8 +/- 2.92	<0.001
MR, $mmHg.s.cm^{-1}$ when FFR≤0.80	**6.25 +/- 3.30**	**5.90+/- 3.90**	**<0.001**
MR, $mmHg.s.cm^{-1}$ when iFR≤0.89	**5.09 +/- 11.8**	**4.63 +/- 11.8**	**<0.001**
Wave Free MR, $mmHg.s.cm^{-1}$	4.48 +/- 2.44	4.05 +/- 2.66	<0.001
iFR	0.90 +/- 0.11	0.89 +/- 0.12	0.073
Pd/Pa	0.92 +/- 0.08	0.92 +/- 0.08	0.110
BSR	0.56 +/- 0.83	0.52 +/- 0.71	0.192

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Highlights

- In recent years, there has been growing role for indices measured at rest, such as iFR.
- These indices may theoretically be more susceptible to resting variation in microvascular tone.
- We show resting coronary flow varies significantly with normal catheter laboratory stimuli
- Resting flow variability is accompanied by significant change in microvascular resistance
- Associated changes in resting indices were statistically and clinically insignificant.

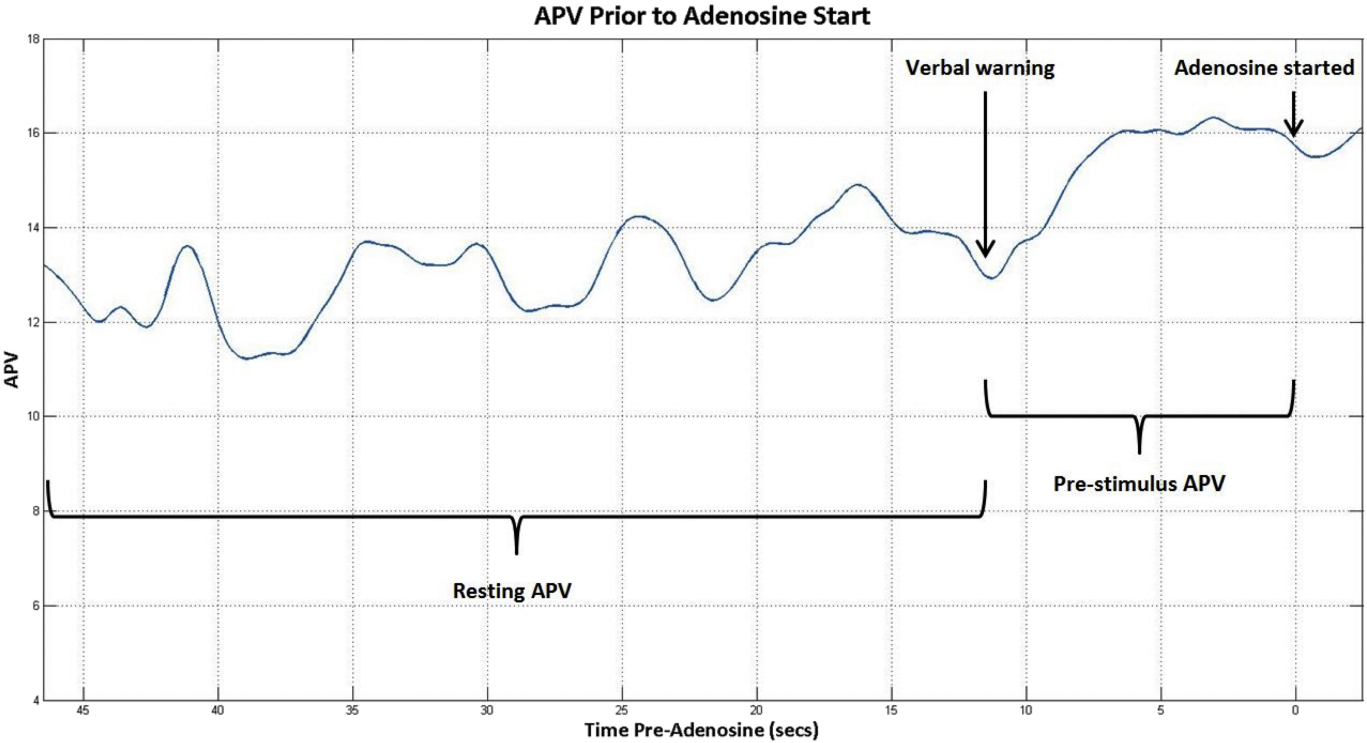
APV Prior to Adenosine Start
Verbal warning
Adenosine started
APV
Pre-stimulus APV
Resting APV
Time Pre-Adenosine (secs)
18
16
14
12
10
8
6
4
45
40
35
30
25
20
15
10
5
0

Figure 1

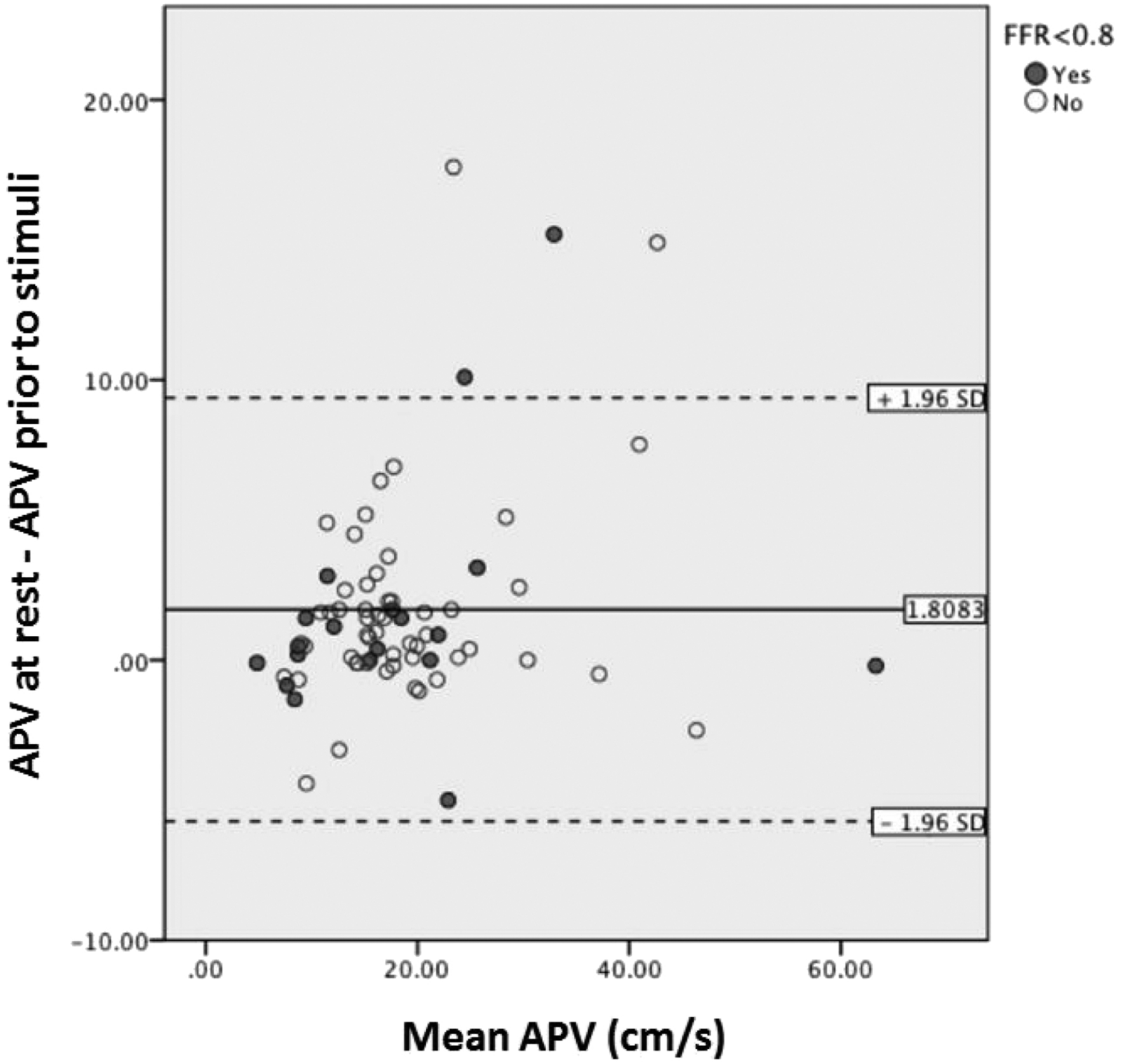
FFR<0.8
Yes
No
20.00
10.00
.00
-10.00
+ 1.96 SD
1.8083
- 1.96 SD
.00
20.00
40.00
60.00
APV at rest - APV prior to stimuli
Mean APV (cm/s)

Figure 2